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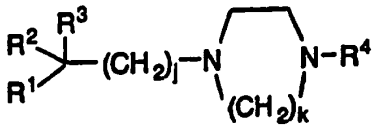
(54) Title: DIARYLALKYL CYCLIC DIAMINE DERIVATIVES AS CHEMOKINE RECEPTOR ANTAGONISTS

(57) Abstract

Cyclic diamines of formula (I) or their pharmacologically acceptable acid addition salts, and their medical applications are described. These compounds inhibit the action of chemokines such as MIP-1a and/or MCP-1 on target cells, and are useful as a therapeutic drug and/or preventative drug in diseases, such as atherosclerosis, rheumatoid arthritis, and the like where blood monocytes and lymphocytes infiltrate into tissues.



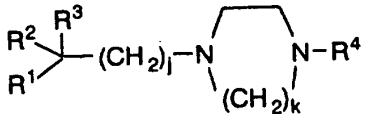
(I)

r is not 0 and $A^3$ is not a single bond or -CO-.

Furthermore, if $R^3$ represents a hydrogen atom and k represents 2, $R^7$ is not unsubstituted; m is not 0 and $R^{11}$ is not a substituted or unsubstituted phenyl group.

If $R^3$ is a cyano group, $R^7$ is not unsubstituted, and the substituent groups for $R^7$ are not halogen atom, $C_1$-$C_6$ lower alkyl group or $C_1$-$C_6$ lower alkoxy group.]

The present invention provides a method of inhibiting the binding of chemokines to the receptor of a target cell and/or a method to inhibit its action onto a target cell using a pharmacological formulation containing as an active ingredient, a cyclic diamine derivative or its pharmacologically acceptable acid adduct (Invention 2) represented by the formula [II] below:



[II]

[wherein $R^1$ and $R^2$ are identical to or different from each other representing a phenyl group or an aromatic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, in which the phenyl or aromatic heterocyclic group may be substituted by any number of halogen atoms, hydroxy groups, $C_1$-$C_6$ lower alkyl groups, $C_1$-$C_6$ lower alkoxy groups, phenyl groups, benzyl groups, phenoxy groups, methylenedioxy groups, $C_1$-$C_6$ hydroxyalkyl groups, carboxy groups, $C_2$-$C_7$ alkoxycarbonyl groups, $C_2$-$C_7$ alkanoylamino groups, dioxolanyl grpoups, or by group represented by the formula: ~~$NR^5R^6$, or else may~~ be condensed with a benzene ring to form a condensed ring, furthermore above substituents for the phenyl or aromatic heterocyclic group and the condenced ring condenced with a benzene ring are optionally substituted by any ssubstituents independently selected from halogen atoms, hydroxy groups, or $C_1$-$C_6$ lower alkoxy groups, and $R^5$ and $R^6$ may be identical to or different from each other representing hydrogen atoms, $C_1$-$C_6$ lower alkyl groups, or $C_2$-$C_6$ lower alkenyl groups;

$R^3$ represents a hydrogen atom, hydroxy group, cyano group, $C_1$-$C_6$ lower alkoxy group or $C_2$-$C_7$ lower alkanoyloxy group;

j represents an integer of 0-3;

k represents 2 or 3 ;

$R^4$ is a group represented by :

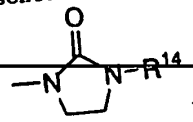
1) Formula: $-A^1-R^7$

(in the formula, $R^7$ represents a phenyl group which may be substituted by any number of the same or different {halogen atoms, hydroxy groups, amino groups, $C_1$-$C_6$ lower alkyl groups, $C_1$-$C_6$ lower alkoxy groups, cyano groups, nitro groups, trifluoromethyl groups, $C_2$-$C_7$ alkoxycarbonyl groups, $C_2$-$C_7$ alkanoyl groups, $C_1$-$C_6$ alkylsulfonyl groups, trifluoromethylsulfonyl groups, phenylsulfonyl groups (which may be substituted with a hydroxy group), 1-pyrrolylsulfonyl groups, $C_1$-$C_6$ hydroxyalkylsulfonyl groups, $C_1$-$C_6$ alkanoylamino groups, or a group represented by the formula: $-CONR^8R^9$) in which $R^8$ and $R^9$, identical to or different from each other, represent hydrogen atoms or $C_1$-$C_6$ lower alkyl groups; $A^1$ is a group represented by the formula: $-(CH_2)_m-$ or a group represented by formula: $-(CH_2)_p-G-(CH_2)_q-$ in which G represents $G^1$ or $G^2$; $G^1$ represents -O-, -CO-, $-SO_2-$, -CO-O-, -CONH-, -NHCO-, -NHCONH-, or $-NH-SO_2-$; $G^2$ represents $-(C=NH)NH-SO_2-$, -CO-NH-NH-CO-, $-CO-NH-NH-CO-NR^{10}-$, $-CO-NH-CH_2-CO-$, $-CO-NH-NH-SO_2-$, or $-CO-N(CH_2-CO-OCH_3)-NH-CO-$; $R^{10}$ represents a hydrogen atom or a phenyl group; m is an integer of 0-3; p is an integer of 1-3; q represents 0 or 1);

2) Formula: $-A^2-R^{11}$

(wherein $A^2$ represents -CO- or $-SO_2-$; $R^{11}$ represents:

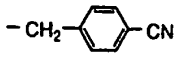
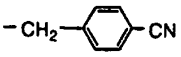
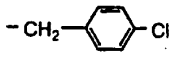
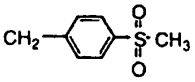
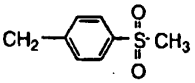
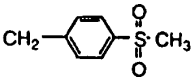
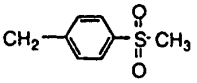
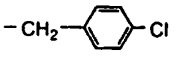
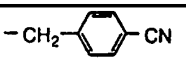
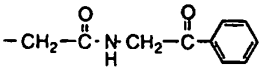
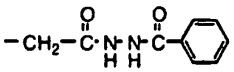
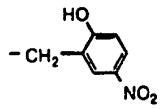
a) A phenyl group which may be substituted by any number of the same or different {halogen atoms, $C_1$-$C_6$ lower alkyl groups, $C_1$-$C_6$ lower alkoxy groups, groups represented by formula $-CH_2-NR^{12}R^{13}$ or groups represented by the formula:



),

b) An aromatic monocyclic heterocyclic group having 1-3 heteroatoms, selected from oxygen atoms, sulfur atoms, and/or nitrogen atoms, and optionally substituted with any of the same or different number of {halogen atoms, $C_1$-$C_6$ lower alkyl groups, $C_1$-$C_6$ lower alkoxy groups}, or

Table 1.1

| Compound No. | $R^1$ | $R^2$ | $R^3$ | j | k | $R^4$ |
|---|---|---|---|---|---|---|
| 1 |  |  | CN | 2 | 2 |  |
| 2 |  |  | CN | 2 | 3 |  |
| 3 |  |  | CN | 2 | 3 |  |
| 4 |  |  | CN | 2 | 3 |  |
| 5 |  |  | H | 0 | 3 |  |
| 6 |  |  | H | 1 | 3 |  |
| 7 |  |  | H | 2 | 2 |  |
| 8 |  |  | H | 2 | 2 |  |
| 9 |  |  | H | 2 | 2 |  |
| 10 |  |  | H | 2 | 2 |  |
| 11 |  |  | H | 2 | 2 |  |
| 12 |  |  | H | 2 | 2 |  |